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ORIGINAL ARTICLE

High preoperative ratio of blood urea nitrogen to creatinine increased mortality in gastrointestinal cancer patients who developed postoperative enteric fistulas

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Abstract Development of an enteric fistula after surgery is a major therapeutic complication. In this study, we retrospectively examined the potential relationship between preoperative laboratory data and patient mortality by collecting patient data from a tertiary medical

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Enteric fistula;
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center. We included patients who developed enteric fistulas after surgery for gastrointestinal (GI) cancer between January 2005 and December 2010. Patient demographics and data on preoperative and pre-parenteral nutritional statuses were compared between surviving and deceased patients. Logistic regression analysis and receiver operating characteristic (ROC) curves were used to determine the predictors and cut-off values, respectively. Patients with incomplete data and preoperative heart, lung, kidney, and liver diseases were excluded from the study; thus, out of 65 patients, 43 were enrolled. Logistic regression analysis showed that blood urea nitrogen-to-creatinine (BUN/Cr) ratio [$p = 0.007$; OR = 0.443, 95% confidence interval (CI), 0.245—0.802] was an independent predictor of mortality in patients who developed enteric fistulas after surgery for GI cancer. In conclusion, the results of our study showed that a high preoperative BUN/Cr ratio increases the risk of mortality in patients who develop enteric fistulas after surgery for GI cancer.

Introduction

Development of an enteric fistula after surgery is a major therapeutic complication [1]. Although most patients receive conservative treatment, such treatments may sometimes fail and reoperation may be necessary, resulting in poor prognosis. With improved nutritional support, infection control, and adequate surgical intervention [2], mortality rates have decreased from 40—65% to 5.3—21.3% in the past few decades [3—9]. Gastrointestinal (GI) cancer generally develops in the elderly; these patients show malnutrition or a combination of medical problems before surgery, which complicates postoperative care and increases the morbidity and mortality rates of these patients. Some of these patients may have received chemotherapy and radiotherapy before surgery, which may worsen the prognosis if complications such as enteric fistulas develop. Although nutritional support and antibiotic treatments have improved outcomes in most of the cases with postoperative complications [10,11], the effectiveness of these approaches in GI cancer patients with postoperative enteric fistulas is largely unknown. Most GI cancer patients can survive after surgery even if enteric fistulas develop. The objective of this study was to identify the risk factors for mortality in GI cancer patients with postoperative enteric fistulas.

Patients and methods

Patients

We collected data from patients who developed enteric fistulas after surgery for GI cancer between January 2005 and December 2010. The study was conducted in a tertiary medical center with 1200 beds in central Kaohsiung. The study protocol was approved by the institutional review board of Kaohsiung Medical University. Patients who had primary cancers such as esophageal, gastric, and colorectal cancers were eligible for surgery. However, those with a medical history of chronic heart failure (CHF), liver cirrhosis, severe chronic obstructive pulmonary disease, and end-stage renal disease requiring regular hemodialysis were excluded. Patients who had undergone radiotherapy and chemotherapy before surgery were also excluded. We also excluded patients with conflicting, ambiguous, or missing data. Parenteral nutrition therapy was administered for achieving the daily caloric requirement if any of the included patients developed enteric fistulas. A support team was in charge of evaluating and monitoring the nutritional therapy, the patient's physical status, and comprehensive data collection. The daily energy requirement of each patient was calculated using the Harris—Benedict equation and adjusted by multiplying with activity and stress factors. The protein supplementation was approximately 1.5—2.0 g/kg/day. The support team evaluated all the nutritional requirements in these patients. All physicians and staff members were blinded to the study design and methods.

During the course of treatment, similar eligibility criteria were used to administer parenteral nutrition therapy. The diagnosis of enteric fistula was confirmed when the drainage amount increased with respect to intestinal contents; consequently, parenteral nutrition therapy was given along with antibiotics according to the patient's clinical status. Patients were divided into two groups: those who survived with spontaneous closure of enteric fistulas and those who expired due to sepsis caused by complications during treatment.

Patient demographics and preoperative medical history included gender, age, diagnosis of primary GI-tract cancer, Union of International Cancer Control (UICC) stage of the cancer, presence of medical conditions, mortality, duration, and complications with parenteral nutritional supplement were recorded by a senior member of the support team. The data collected by the support group was rechecked by a senior physician. The patients' laboratory test data were obtained as per routine procedures performed before surgery [determination of white blood cell (WBC) count, and tests for glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), blood urea nitrogen (BUN), and creatinine (Cr)]; further, standardized total parenteral nutrition (TPN) was started at our hospital. Total protein (TP), albumin, and globulin were measured before starting TPN. Cockroft—Gault formula was used to estimate the patients' glomerular filtration rates (GFRs).

Statistical analysis

Normally distributed data were presented as mean ± standard deviation values. Categorical variables were

analyzed using χ^2 and Mann–Whitney *U* tests. Logistic regression analysis was performed to determine the predictors of mortality in patients with complications caused by enteric fistula. In the logistic forward regression model, we represented the magnitude of association between the dependent variable and each independent variable by obtaining odds ratios (OR) and 95% confidence intervals (CI). Model fit was determined using standard likelihood ratio tests. Data analyses were performed using SPSS software (Version 15; SPSS Inc., Chicago, IL, USA). Two-tailed *p* values less than 0.05 were considered statistically significant. The diagnostic values of different variables and the best cut-off values were determined using receiver-operating characteristic (ROC) curves. The cut-off value for each variable was set at the points representing the highest accuracy of analysis (minimal false negative and false positive results).

Results

During the study period, 65 patients were diagnosed with enteric fistula after surgery for GI cancer. Three patients receiving neoadjuvant chemotherapy, two receiving preoperative radiotherapy, four with medical history of liver cirrhosis, three with undetermined pathology reports, and 10 with incomplete data were excluded. Thus, 43 patients were enrolled in the study.

Demographic data of these 43 GI-tract cancer patients are presented in Table 1. Sixteen patients died (eight men and eight women; mean age, 61.81 ± 17.44 years), and 27 survived (20 men and seven women; mean age, 62.67 ± 10.60 years). There was no significant intergroup difference in the types of GI cancers ($p = 0.523$). No intergroup differences were noted in the number of cases of diabetes mellitus ($p = 0.614$). In the preoperative laboratory data, only BUN values were significantly different between the two groups ($p = 0.001$). Preoperative GFR did not significantly differ between the two groups ($p = 0.182$).

All variables in the univariate analyses were analyzed in a logistic forward regression model. The BUN/Cr value ($p = 0.007$; OR = 0.443, 95% CI, 0.245–0.802) was identified as an independent predictor of mortality. The model adequately fitted the data with the Hosmer–Lemeshow statistics ($p = 0.926$), while 74.5% of the variation could be explained by the Nagelkerke R square model (Table 2). A cut-off BUN/Cr value of 17 would have permitted the sensitivity and specificity to be 84.2% and 79.4%, respectively (area under ROC curve, 0.848) (Fig. 1).

Discussion

Preoperative laboratory analyses in primary GI cancer patients requiring surgery, would be useful to predict the mortality caused by postoperative enteric fistulas. In this study, we found that patients with a higher BUN/Cr value had a higher average mortality rate (37.21%); hence, preoperative BUN/Cr ratio could be used to predict postoperative mortality in cases showing enteric fistulas.

To reduce the bias that may have influenced the results of surgery, we focused on patients with only primary GI cancers; to this end, patients with preoperative medical conditions, including liver cirrhosis, uremia, and CHF, were excluded. The uniformity in the pre-operative status of the patients reflected in their preoperative laboratory data, which showed similar serum TP, albumin, and globulin levels. In addition, the other preoperative data (WBC, GOT, GPT, and Cr) showed no intergroup differences. Furthermore, although preoperative serum BUN level was different between the two groups, preoperative GFR levels showed no significant difference. This meant that the renal function of patients in the two groups did not statistically differ.

Table 1 Clinical characteristics of the primary gastrointestinal (GI) cancer with postoperative enteric fistula.

	Survival group ($n = 27$)	Mortality group ($n = 16$)	*p*
Age (y), mean ± SD	62.67 ± 10.60	61.81 ± 17.44	0.861
Sex, no. of women (%)	7 (25.9%)	8 (50%)	0.109
Primary GI cancer			
Esophageal cancer	1	2	0.523
Gastric cancer	8	5	
Colorectal cancer	18	9	
Diabetes (Y/N)	22/5	12/4	0.614
Laboratory data (normal range)			
BUN (7–20 mg/dL)	12.73 ± 4.67	22.16 ± 9.16	0.001
Cr (0.8–1.4 mg/dL)	0.91 ± 0.22	0.95 ± 0.30	0.600
GOT (1–21 units/L)	32.96 ± 16.35	27.92 ± 16.32	0.367
GPT (7–27 units/L)	32.81 ± 30.16	32.96 ± 16.35	0.249
Total protein (g/dl)	6.00 ± 0.53	6.12 ± 0.86	0.630
Globulin (g/dl)	2.82 ± 0.44	3.02 ± 0.62	0.245
Albumin (g/dl)	3.18 ± 0.52	3.11 ± 0.48	0.652
WBC (4.3–10.8 × 10^3/mm^3)	12162.71 ± 6540.23	9266.45 ± 4063.89	0.071
Glomerular filtration rate	70.28 ± 23.39	62.39 ± 23.92	0.182
BUN/Cr (10:1–20:1)	14.00 ± 4.82	22.00 ± 6.57	<0.001

BUN = blood urea nitrogen; Cr = creatinine; GOT = glutamic-oxaloacetic transaminase; GPT = glutamic-pyruvic transaminase.

Table 2 Independent risk factors associated with mortality of enteric fistula.*

	OR	95% CI	*p*
BUN/Cr	0.443	0.245—0.802	0.007
Age	0.889	0.780—1.013	0.077

*The risk factors included in the logistic regression model were gender, glomerular filtration rate (GFR), blood urea nitrogen (BUN), creatinine (Cr), diseases, Diabetic mellitus (DM), glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), Total protein (TP), albumin, and globulin. The *p* value of BUN/Cr was <0.05.

Although there have been recent advances in nutritional therapy, infection control, and surgical techniques, enteric fistulas are a major cause of morbidity and mortality [1]. Correction of intravascular volume deficit, drainage of abscesses, and control of fistula effluent are the primary procedures in enteric fistula management [12]. Serum albumin level less than 3.0 g/dL, high-output fistulas with hydroelectrolytic deficit at diagnosis, multiple fistulas, jejunal site, sepsis, and complex fistulous tracts were associated with patient mortality [13,14]. Therefore, management of the intravascular volume is important for patient management. The cut-off value of 17 estimated by using the ROC curve may provide the strategy for fluid supply.

An increased BUN/Cr value along with decrease in the effective circulating blood volume is found in patients with renal disease, congestive heart failure, gastrointestinal bleeding, and acute urinary tract obstruction [15—17]. High BUN/Cr values also indicate an increased risk of hospitalization and all-cause mortality in patients with CHF [18,19].

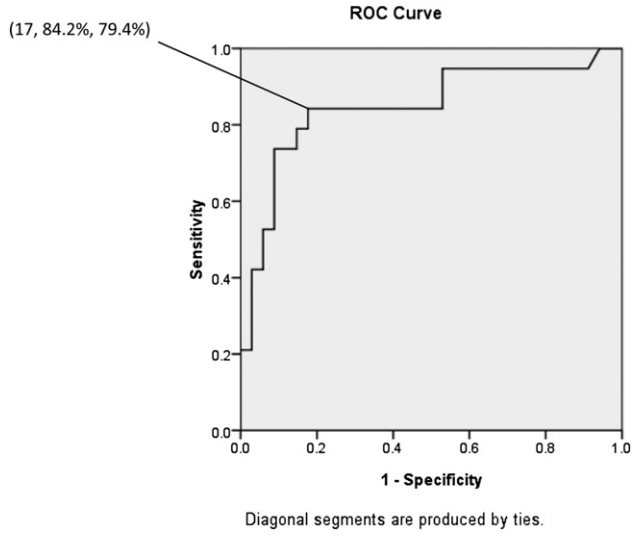

Figure 1. Receiver-operating characteristic (ROC) curves of the blood urea nitrogen-to-creatinine (BUN/Cr) ratio in the prediction of mortality rate of 43 gastrointestinal (GI)-tract cancer patients with postoperative enteric fistulas. One of the ROC plots with a cut-off value of 17 for BUN/Cr ratio was selected for mortality prediction. The plot is highlighted; figures in parentheses indicate sensitivity and specificity. The area under the ROC curve is 0.848 [95% confidence interval (CI), 0.726—0.969].

We found higher mortality rates in patients with higher ratios in the group with post-surgical enteric fistulas. Because we excluded patients with heart failure, renal disease, urinary tract obstruction, and preoperative GI bleeding, the increased BUN/Cr ratio could be attributed to preoperative dehydration. Postoperative management of enteric fistula is important for patient survival. Therefore, more standardized procedures are applied to manage such complications. The postoperative management of our patients was consistent, which reduced bias caused by different postoperative management options. The significant intergroup difference in preoperative BUN/Cr values merely represented the difference in BUN values. Patients with high-output fistulas have higher mortality rates [14]. Renal function may be an important factor influencing the clinical outcome in cases of fistula development. However, preoperative dehydration might result in renal dysfunction that could eventually deteriorate the patient's condition resulting in higher mortality rates. Therefore, prevention of dehydration is important in the preoperative preparatory phase.

Our study had the following limitations. We could not determine if the patients were on a high-protein diet before the operation or showed muscle wasting. However, serum TP, albumin, and globulin levels did not show any difference between the two groups, which might indicate that the preoperative nutritional status did not affect the clinical outcome. Although the BUN/Cr ratio may reveal the effective preoperative circulating blood volume, a high ratio may be a surrogate marker of other differences. Furthermore, there was no difference between the two groups in renal function tests (except the serum BUN level); however, we think prevention of iatrogenic injury to the kidneys and assessment of renal function are important factors influencing the mortality rates after enteric fistula development. Some important factors were not analyzed owing to the retrospective nature of the study. Previous studies have corroborated our finding of high-output fistulas being a risk factor for patient mortality [14]. Therefore, we did not focus on such fistulas. Surgery may be an important factor influencing patient outcome because it is detrimental to patients who lack spontaneous healing, and may introduce a bias in the postoperative procedures. Nutritional status and supply during follow-up could be factors affecting mortality; however, we followed a standard procedure for our postoperative patients.

In this study, we identified the BUN/Cr ratio as an independent risk factor to predict patient survival after postoperative enteric fistula development. We recommend prevention of dehydration prior to surgery in these patients. Additional clinical information is essential to confirm the hypothesis that dehydration may be related to mortality rates. Therefore, further studies are required to investigate if preoperative fluid administration could improve the clinical outcome.

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The first two authors have equally contributed to this study, and therefore, both can be considered first authors. We are grateful to Yen-Ko Lin for help with statistical analyses, and staff of the Division of Gastrointestinal and General Surgery, Department of Surgery, for patient care.

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